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Ultrasound triggering method

Field of the invention

The present invention relates to ultrasound imaging, more particularly to a method of triggered ultrasound imaging of the myocardium wherein the risk of eliciting cardiac arrhythmia is minimized. Further the invention relates to a method of assessing perfusion of the myocardium.

Description of related art

It is well known that contrast agents comprising dispersions of gas microbubbles are particularly efficient backscatterers of ultrasound by virtue of the low density and ease of compressibility of the microbubbles. For example WO 97/29783 describes such microbubble dispersions. If appropriately stabilised microbubbles may permit highly effective ultrasound visualisation of, for example, the vascular system and tissue microvasculature, often at advantageously low doses.

The following patent relates to ultrasound imaging involving contrast agent destruction. It is stated in US-A-5425366 that certain types of microparticulate ultrasound contrast agents, for example gas-containing polymer microcapsules, may be visualised by colour Doppler techniques despite being essentially motionless, e.g. as a result of uptake by the reticuloendothelial system. It is proposed that the relatively high insonication energy levels associated with colour Doppler investigations cause the microparticles to burst, thereby generating Doppler-sensitive signals described as "acoustically stimulated acoustic emission". It will be appreciated that since this technique is concerned exclusively with detection of essentially motionless contrast agent microparticles it is inherently inapplicable to measurement of rates of perfusion. Triggering techniques are not described.

WO 98/47533 is based on the finding that ultrasound imaging involving ultrasound-induced destruction or modification of contrast agents may be used to give a measure of tissue perfusion. The method described uses a first high energy ultrasound pulse or series of pulses to destroy or discernibly modify a recognisable

amount of the contrast agent within a target region, but rather than employing subsequent pulses to detect background signals to be subtracted from the first detection sequence the method uses the subsequent pulses to detect the flow of "fresh" or unmodified contrast agent (and therefore blood) into the target region. This permits determination of parameters such as vascular blood volume fraction, mean transit time and tissue perfusion with respect to local vascular state within the target region. The initial high energy pulse or pulses may, for example, be used to clear a closely defined target region of detectable contrast agent so that a sharp front of further contrast agent, which is readily detectable and quantifiable by ultrasound imaging, then flows into this region. ECG-triggering is only mentioned as one of several techniques, without any further specifications. Ultrasound machines capable of destruction-wash-in techniques, also known as perfusion imaging, use a first high energy ultrasound pulse or series of such pulses, that is, destruction pulses with a high mechanical index (MI), to destroy the contrast microbubbles e.g. in the myocardium, and then demonstrate the wash-in of microbubbles in the myocardium by imaging using low energy pulses (low MI).

Ultrasound triggering methods of the myocardium have been described by Van der Wouw et al. in J Am Soc. Echocardiogr. 13: 288-294, 2000 and by Van der Wouw et al. in European Heart Journal 20: 683, 1999. Generally, triggered ultrasound imaging is primarily used to minimize the ultrasound destruction of gas microbubbles and to make the visual judgement of myocardial contrast wash-in easier than during live imaging. During live imaging, the variations in base-line contrast are often higher than the contrast build-up during wash-in, hence live imaging is little, if at all, useful for assessment of myocardial perfusion. The imaging modes, e.g. second harmonic, pulse inversion, ultra-harmonic and power modulation, used during imaging of ultrasound contrast agents take advantage of the non-linear properties of the gas microbubbles. However, as second harmonic, pulse inversion and ultra-harmonic imaging use a lower transmit frequency, they are often more destructive towards microbubbles than standard B-mode imaging at comparable mechanical index. Van der Wouw et al. report that trigger-related ventricular premature beats (VPBs) in humans and animals are elicited during ultrasound imaging with the triggered interval sequencing (TIS) technique and ultrasound contrast agent administration.

Technically, triggered imaging is a technique wherein the ultrasound machine is synchronized with the echocardiogram (ECG) of the heart, or similar cardiac-synchronous signal, or with a clock signal. When the ECG signal is used as triggering rhythm, a single or a given low number of frame(s) is taken at the same predetermined phase of the ECG cycle, either at every heart beat (trigger interval 1:1) or at a specified interval every n^{th} heart beat (trigger interval 1:n). The heart rhythm is divided into systole and diastole. Systole represents the period in which the ventricles contract, while diastole represents the period in which the ventricles are relaxed and dilated. Atrial contractions fill the heart during end-diastole. The P-wave of the ECG signal represents atrial contractions and the end of the diastole. The R-wave of the ECG signal represents initiation of ventricular contractions during start-systole. The R-wave is the amplitude that is recognized easiest and most consistent by ultrasound machines and by adjusting the trigger delay (time of ultrasound trigger in relation to the R-wave), the actual trigger point can be adjusted throughout the length of the ECG cycle. In humans, end-systolic triggered (EST) imaging use triggering approximately at the T-wave, about 300 msec after the R-wave, and image the heart during maximal contraction. EST is most often used during triggered imaging, as the heart is most contracted during this phase of the ECG cycle. More of the heart will therefore be in the imaging sector, the myocardium is thickest and the degree of shadowing in the ventricle is minimized during EST. In order to image myocardial perfusion, the contrast agent present in the myocardium has to be destroyed before the wash-in of new microbubbles can be observed. Destruction of the gas microbubbles require high-energy ultrasound pulses (high MI) and when high MI is used during end-systolic triggering, cardiac arrhythmia, such as ventricular premature beats (VPB), may occur in relation to triggering. ECG triggered, contrast enhanced ultrasound imaging of the heart can elicit VPBs and other rhythm disturbances of the heart at high mechanical index (MI) levels. Trigger-induced arrhythmia occurs primarily during end-systolic triggering, which is the most relevant time of the ECG cycle to image during contrast administration. In triggering methods both the high-energy pulses and the imaging of wash-in are triggered imaging, normally using second harmonic or pulse inversion or some other non-linear imaging technique. TIS, the technique used by Van der Wouw et al, is a triggering technique wherein the imaging pulses

are also destruction pulses, both using high-energy pulses. TIS can be used at any given point in the ECG cycle, but is most often used during end-systole. Mycocardial perfusion is assessed by varying the trigger interval and observing for regional differences in the trigger intervals needed before the maximum contrast "returns" in all myocardial regions. Longer trigger intervals will be needed in myocardial regions with decreased perfusion compared to regions with normal perfusion. The identical high mechanical index of destruction and imaging pulses precludes imaging of contrast build-up due to considerable microbubble destruction. The number of high-energy end-systolic triggered imaging pulses during a clinical procedure of TIS is consequently very high, increasing the risk of eliciting VPBs.

There is a need for methods that permit better evaluation of coronary artery disease, and particularly measurements of tissue perfusion. Measurements of blood flow per unit of tissue mass, are of value in, for example, detection of regions of low perfusion, e.g. as a result of arterial stenosis. Measurement of cardiac perfusion in order to identify any myocardial regions supplied by stenotic arteries is of particular importance. The current invention is directed towards the use of ultrasound contrast agents, i.e. dispersions of microbubbles, in an ultrasound imaging triggering method for imaging of the myocardium, and particularly for perfusion assessments. It is important to define and refine ultrasound imaging triggering techniques to give methods that do not result in arrhythmia. A method of triggered ultrasound imaging of the myocardium avoiding or minimizing the risk of arrhythmia has been sought.

Summary of the invention

The following invention provides a method of triggered ultrasound imaging, for imaging of the myocardium wherein cardiac arrhythmia, such as ventricular premature beats, is minimized.

It has surprisingly been found that a method of triggered ultrasound imaging of the myocardium of a human or non-human animal subject administered with an ultrasound contrast agent wherein at least one high mechanical index ultrasound pulse sequence is initiated such that the first pulse of said sequence falls within the

Q-R-S interval of the echocardiogram of the myocardium, is useful. According to the invention pulses with high mechanical index are hence triggered at start-systole.

A further aspect of the invention is use of an ultrasound contrast agent in the manufacture of an image-enhancing composition for administration to the vascular system of a subject in order to measure or assess the perfusion of the myocardium using a method wherein at least one high mechanical index ultrasound pulse sequence is initiated such that the first pulse of said sequence falls within the Q-R-S interval of the echocardiogram of the myocardium.

The main advantage of the invention is that start-systolic triggering of destruction pulses according to the invention is unlikely to elicit arrhythmia, such as VPBs. Start-systolic destruction pulses do not affect the efficacy of subsequent end-systolic imaging pulses, which do not elicit VPBs due to the low MI needed.

Brief description of the drawings

Figure 1 illustrates the probability of ventricular premature beats versus triggering delay during ultrasound infusion to dogs, using Triggered Interval Sequencing (TIS) imaging, in relation to the ECG of the heart.

Figure 2 illustrates the myocardial membrane action potential recording the changes in electrical potential across the membrane.

Figures 3 and 4 give graphical presentations of existing triggering techniques and the non-arrhythmogenic Destruction-Wash-In Imaging (DWI)/Triggered Replenishment Imaging (TRI) and Real-Time Perfusion Imaging (RTPI) techniques of the invention.

Detailed description of the invention

A first aspect of the invention is a method of triggered ultrasound imaging of the myocardium of a human or non-human animal subject administered with an ultrasound contrast agent wherein at least one high mechanical index ultrasound pulse sequence is initiated such that the first pulse of said sequence falls within the Q-R-S interval of the echocardiogram of the myocardium.

The method is carried out by administering a subject with an ultrasound contrast agent such that this agent is uniformly distributed in the blood pool, and subjected to ultrasound emission, e.g. from a scanner directed at the heart, in order to destroy or discernibly modify the circulating contrast agent. Abrupt termination of the ultrasound emission will give a substantially sharp bolus front as further contrast agent is washed in, and this may be used for assessment of the perfusion in the coronary arteries. Perfusion may be defined as a measurement of blood volume per tissue weight and unit time. The degree of regional perfusion may be assessed by monitoring the temporal development of contrast effect in different regions of tissue upon arrival of the created bolus. The arrival of contrast to tissue regions of high perfusion is expected to take place earlier than in areas of lower perfusion.

The composition of the heart can basically be divided in pacemaker cells and normal myocardial cells. The interior of myocardial cells is normally negative compared to the outside environment, with a resting membrane potential of -80 to -90 mV, that instantaneously increase to 20-30 mV during depolarization. If not excited by external (electrical) stimuli, the increase in resting membrane potential (RMP) is very slow during depolarization, i.e. in practice almost stable, in normal myocardial cells, while in pacemaker cells the RMP automatically increases such that when the threshold potential (TP) of about -60 mV is reached, the cell depolarizes. Following depolarization to a membrane potential of 20-30 mV, the membrane potential decreases to the resting membrane potential in 4 phases, as shown in figure 2. This figure shows myocardial membrane potential measured by placing an electrode inside a muscle cell and then recording the changes in electrical potential (millivolts) that occur across the membrane over time (seconds). In phase 1, the plateau phase after depolarization, the membrane potential is more or less unchanged, while a slow decrease is initiated during phase 2. The membrane potential decrease further in phase 3, where the threshold potential (TP) is passed, before the normal resting membrane potential is regained in phase 4. During phases 1, 2 and 3, until threshold potential is passed, the myocardial tissue is refractory to any external stimuli, while the time from threshold potential passage (in phase 3) and until phase 4 is relatively refractory and is excitable if stimulus is sufficiently high. Referring to the ECG-cycle shown in figure 1, during the normal ECG cycle, the P-wave represents the depolarization

of the atria while the isoelectric period between the P–wave and the R-wave represents the delayed passage of the atrial impulses through the atrioventricular node. The ventricular depolarization is composed of 3 main phases, represented by the Q-, R- and S-wave. The Q-wave represents the first phase of ventricular depolarization (mid- and apical portions of ventricular septum) while the R-wave represents the propagation of the electrical impulse from the sub-endocardial terminations of the Purkinje fibers to the epicardial surface (free walls) of both ventricles. The S-wave represents the depolarization of the muscle fiber at the ventricular basis while the T-wave represents the ion shifting during repolarization of the myocardial cells.

When the above membrane potential characteristics of single myocardial cells are applied to the heart, the ventricles are refractory to external stimuli during depolarization and the time immediately following depolarization. The Q-R-S interval and a short period thereafter, until threshold potential is regained, is therefore the refractory period of the heart. In figure 1 this refractory period is denoted A. We have now found that it is favorable to use an ultrasound triggering method wherein pulses with high mechanical index are initiated during this refractory period, because eliciting of any ventricular premature beats is avoided or minimized.

It has been found that it is the time of initiation of the destruction pulse sequence, rather than the length, MI, frame-rate or pulse length of the destruction pulse sequence, that determines whether ventricular premature beats are elicited.

In a preferred embodiment of the invention high MI destruction pulse sequences are initiated at the beginning of the refractory period, i.e. in the Q-R-S interval and continued until just before the first, second or any later end-systole after initiation, to avoid VPBs.

The high mechanical index pulses are applied to destruct or discernibly modify ultrasound contrast agent. Preferably the first high mechanical index ultrasound pulse coincides with the R-wave of ECG of the myocardium and more preferably the high MI pulse sequence persist throughout the ECG cycle. More preferably,

the sequence of high mechanical index pulses should be adjusted according to the heart rate such that it stops just before a T-wave of the ECG, and most preferably, it should stop just before the T-wave of the next ECG-sequence. This will minimize inflow of contrast microbubbles from end of the destruction pulses until imaging of contrast wash-in is initiated. At the same time as the sequence of high mechanical index pulses stops low MI imaging pulses are preferably initiated.

In yet a preferred embodiment further low mechanical index imaging pulses are initiated at a T-wave. As described, triggered imaging pulses should be end-systolic (EST), but as they use a mechanical index well below the lowest mechanical index where trigger-related VPBs have been observed, no effects on cardiac rhythm are expected. The high-energy destruction pulses initiated at the R-wave are hence followed by low energy imaging pulses initiated at the T-wave. The imaging pulses are preferably initiated at a T-wave, but initiation at other points of the ECG may be done. The destruction pulses should then end at the same random point. Preferably the imaging pulses are initiated at the first T-wave immediately following the high mechanical index pulses. Such imaging pulses may be triggered, as shown in figure 3C with triggering at every heart beat, or may be continuous as shown in figure 4E. In order to assess perfusion one would preferably look at a sequence of images, but a single parametric perfusion image is also a possibility.

The energy level of the initial ultrasound destruction pulses is high and should have a mechanical index high enough to destroy or modify the contrast agent present in the imaging plane. This MI level will vary depending on the contrast agent used and the patient imaged, but typically the MI will be of at least 0.2-1.9, and preferably between 0.7-1.4. The imaging pulses should have a mechanical index low enough to image the contrast agent without destroying it or with a minimum destruction. The MI level will again vary from agent to agent, but the level will typically be of 0.1-1.0, and preferably between 0.2-0.6.

The destruction pulses must be applied long enough to destroy the contrast agent in the imaging plane and ending as close as possible to the first low MI imaging pulse. This could be any duration, from one single ultrasound frame to several

seconds. The destruction pulses will typically be sent out at the scanners regular frame rate, but since the information in these images is generally discarded the frame rate may be increased at the expense of image quality. The length of the destruction pulses may also be increased to improve the destruction of the ultrasound contrast agent.

Any ultrasound triggering method may be used, subject to that the initial destruction pulse falls within the Q-R-S-interval, or coincides with the R-wave, of the ECG. The following imaging modes may be used; fundamental (B-mode), second (or any higher) harmonic, sub-harmonic, cadence contrast agent imaging, coherent pulse sequencing, pulse/phase inversion, ultraharmonic, power modulation, power pulse inversion and power contrast imaging and any combination of these techniques. Preferred techniques are destruction-wash-in imaging (DWI), triggered replenishment imaging (TRI) and real-time perfusion imaging (RTPI).

Myocardial triggering ultrasound techniques can be divided into three main categories, all using high-energy ultrasound pulses for gas microbubble destruction. Current use of these three techniques may all elicit trigger-related arrhythmia such as VPBs. TIS and DWI/TRI trigger according to the ECG cycle, while the third, RTPI, trigger manually. DWI and TRI are relatively identical triggering techniques. The destruction pulse sequences are of relatively high mechanical index, while the imaging pulses use low mechanical index. In known methods, both destruction pulses and imaging pulses are triggered at the same point in the ECG cycle, in the end-systole, but different trigger delays of the destruction and imaging pulses are possible. The trigger intervals of destruction pulses and the imaging pulses are variable, with a usual trigger interval of destruction pulse sequences about 1:8 –1:20, while the imaging pulses are triggered every heart beat (1:1). During DWI/TRI an initial continuous sequence of high MI destruction pulses initiated at a certain time of the ECG cycle destroys the microbubbles and the myocardial contrast. Wash-in of the gas microbubble contrast agent is then imaged at low MI by EST imaging at every heartbeat. The number of high MI EST destruction pulse sequences during a clinical procedure is consequently considerably lower with DWI/TRI compared to TIS. However, as

the destruction pulse sequence of DWI/TRI in known methods are initiated during end-systole like the imaging pulses, the possibility of trigger-related arrhythmia during the first pulses of each destruction pulse sequence exist. Real-Time Perfusion imaging (RTPI) is a technique wherein a sequence of high mechanical index destruction pulses is followed by continuous imaging at low mechanical index. The operator manually initiates destruction pulses randomly at any given time during the ECG cycle. Initiation during end-systole may therefore be able to elicit trigger-related arrhythmia.

The probability of eliciting VPBs depends highly on the physical properties of the emitted ultrasound pulses and the imaging plane used. The acoustic energy in each imaging frame, measured at a point in the imaging plane, appears to be a better predictor for VPB frequency than MI, but it is not optimal. There is a part of the heart cycle where it is not possible to elicit VPBs. Changing the imaging protocol from high MI triggered imaging to a flash imaging protocol can make the probability of inducing VPBs extremely low. To minimize the probability of eliciting VPBs it is suggested that perfusion imaging should be performed as a flash imaging procedure, where the destructive flash pulses are initiated at the start of the heart's refractory phase, for instance at the R-wave, and fired continuously until the output is switched to non destructive imaging pulses. For TRI this switch would typically occur in the end systole following the triggering of the flash pulses or in the end systole of the heartbeat thereafter. When using a flash sequence, as opposed to a single, high MI imaging pulse, to destroy the USCA in the imaging plane, the MI for the destructive pulses may be lowered and still give adequate micro bubble destruction.

Existing ultrasound triggering techniques, particularly the TIS technique but also DWI/TRI and RTPI, all include the risks of inducing trigger-related ventricular premature beats (VPB) and other arrhythmia when used for cardiac imaging during infusion of gas microbubble contrast agents. Trigger-related ventricular premature beats (VPBs) in humans and animals during ultrasound imaging using the TIS technique have been reported in the literature and these findings have been confirmed in performed experiments in different animal species. Figure 1 illustrates the probability of ventricular premature beats versus trigger delay

during infusion of an ultrasound contrast agent (Sonazoid®), using a TIS technique and a Philips HDI 5000 US machine with a P3-2 transducer, MI 1.3. At the given time line (approximately 800 msec), a typical ECG of the heart is included in the figure, naming the different waves of the cycle. The figure shows that the probability of ventricular premature beats is highest during end-systole, around the T-wave of the ECG. As can be seen from figure 1, a trigger delay of 0-180 msec, that is the R-S interval plus time needed for repolarisation, results in no VPBs during TIS, while VPBs occur during the remaining ECG cycle (trigger delays of 180-700 msec) and particularly during end-systole (200-240 msec).

Also, during end-systolic triggered (EST) destruction wash-in imaging (DWI) at destruction pulses of MI 1.2 with the Philips HDI 5000 ultrasound machine and a P4-2 transducer, very few, but definitely trigger-related VPBs, were observed in dogs. While some of these differences in VPB incidence between the TIS and DWI/TRI may be related to inherent differences in the nature of the ultrasound transmitted by different transducers, trigger-related VPBs are not excluded when high MI destruction pulses of DWI/TRI and RTPI are started during end-systole.

To avoid the induction of trigger-related VPBs during DWI/TRI and RTPI imaging during infusion of gas microbubble contrast agents, we have found that the destruction pulses and the imaging pulses should be initiated at different points of the ECG cycle. As VPBs are dependent upon myocardial gas microbubble concentration and the first pulses in the high MI destruction pulse sequences are elicited during maximal microbubble concentration, these first pulses of the destruction pulse sequence are the most likely to elicit VPBs. The chance of VPBs per pulse decreases with every pulse of the destruction pulse sequence due to continuous microbubble destruction. It has therefore been found that it is the time of initiation, rather than the length of the destruction pulse sequence, that determines whether VPBs are elicited.

A graphical presentation of the current and the suggested non-arrhythmogenic triggering DWI/TRI and RTPI techniques are included in figures 3 and 4. In these graphs X denotes destruction pulses and Y denotes imaging pulses. Graph A of

figure 3 shows a standard TIS, end-systolic high MI triggering (1:1). The imaging pulses are also destruction pulses. The pulses are applied during end-systole, i.e. at the T-wave. Graph B of figure 3 shows a standard DWI/TRI-technique with end-systolic triggering of high MI destruction pulses (1:8) and end-systolic triggering of low MI imaging pulses (1:1). ATL HDI 5000 and Philips Sonos 5500 are examples of ultrasound machines that may be used in both examples. In both these high MI end-systolic triggered techniques there are risks of eliciting arrhythmia. Graph C of figure 3 illustrates a technique of the invention. Non-arrhythmogenic DWI/TRI, R-wave triggering (i.e. start-systolic) of high MI pulses (1:8) is followed by end-systolic triggering of the low MI imaging pulses (1:1). This new type of non-arrhythmogenic DWI/TRI technique, triggering destruction pulses and imaging pulses at different time points in relation to the ECG, is a technical possibility today with the Philips Sonos 5500 ultrasound machine. Graph D of figure 4 shows a standard real-time perfusion imaging technique (RTPI) with a random initiation of high MI destruction pulses followed by continuous low MI imaging. An ATL HDI 5000 may be used in such technique. Graph E of figure 4 illustrates another technique of the invention. In this non-arrhythmogenic RTPI technique high MI destruction pulses are initiated at the first R-wave, i.e. start-systolic, after a random initiation, and are then followed by continuous low MI imaging. An ATL HDI 5000 may for instance be used. In the techniques of the invention, shown in graphs C and E, the destruction pulses and the imaging pulses are initiated at different points in the EGC. The high MI destruction pulses are initiated at the R-wave (start-systolic), while the low mechanical index imaging pulses are initiated at the T-wave (end-systolic). The graphs A, B and D are shown for comparison.

The preferred time delay between i.v. injection of the ultrasound contrast agent and start of data acquisition (destruction/imaging) is typically in the order of tens of seconds following a bolus injection. For an i.v. infusion of microbubbles the preferred time delay is the time required to reach an approximate steady state of contrast enhancement of the blood. A stable and consistent microbubble concentration throughout the DWI/TRI, RTPI and TIS techniques is a prerequisite for assessing microbubble wash-in as an indication of cardiac perfusion. Start of

data acquisition should therefore not be started until the microbubble concentration is stable, usually 1-10 minutes after start of microbubble infusion.

In principle any free flow ultrasound contrast agent may be used in the method of the invention, subject only to the requirement that the size and stability of the contrast agent moieties are such that they are capable, following intravenous injection, of passing through the lung capillaries and generating responses in the left ventricle of the heart and the myocardial circulation. Contrast agents which comprise or are capable of generating gas microbubbles are preferred since microbubble dispersions, if appropriately stabilised, are particularly efficient backscatterers of ultrasound by virtue of the low density and ease of compressibility of the microbubbles. Ultrasound contrast agents comprising a vector having affinity for a biological target are also enclosed. The ultrasound contrast agents described by the following patent families are relevant for use in the method of the invention, for purposes of illustration and not of limitation: WO97/29783, WO92/17212, WO97/29782, EP 554213, WO-9516467, EP474833, EP 619743, US 5,558,854, WO 92/17213.

Examples of ultrasound contrast agent that may be used according to the invention are, for purposes of illustration and not of limitation, Optison®, Levovist®, Definity®, Imagent®, Sonovue®, Echogen®, Sonogen® and Sonazoid®

A variety of acquisition ways may be used to detect and quantify inflowing contrast agent following the initial ultrasound destruction, e.g. to generate a perfusion related image displaying a time-related measure of in-flowing contrast agent within the target region and thereby permitting discrimination between areas of different perfusion. The desired image may be obtained from analysis of individual scanlines or on a frame by frame basis; the former may be advantageous in areas with high rates of perfusion in order to obtain sufficient numbers of samples to discriminate areas with different perfusion, whereas the latter may be preferred in areas with low rates of perfusion.

The imaging method of the invention may be used in measurement of cardiac perfusion, and this forms a further aspect of the invention. With the triggered ultrasound imaging method of the invention myocardial perfusion assessments, making the visual judgement of myocardial contrast wash-in easier, can be performed with no, or minimal, risk of eliciting ventricular premature heart beats. A further aspect is hence a method of measuring or assessing cardiac perfusion in a human or non-human animal subject comprising administering an effective amount of an ultrasound contrast agent to the subject, insonicating a target region of the myocardium with ultrasound pulse sequences with high mechanical index such that the first pulse of said sequences falls within the Q-R-S interval of the ECG of the myocardium.

Use of an ultrasound contrast agent in a method as described is a further aspect of the invention.

Use of an ultrasound contrast agent in the manufacture of an image-enhancing composition for administration to the vascular system of a human or non-human animal subject in order to measure or assess the perfusion of the myocardium in accordance with the method is yet a further aspect.

Preferably, the subject has been preadministered with an ultrasound contrast agent before the method of the invention is performed.

The invention may be accomplished by modifying the existing software in the ultrasound machines by implementing facilities enabling automatic triggering of high mechanical destruction pulses and low mechanical imaging pulses at different time-points in relation to the ECG. The software should allow for automatic beat per beat adjustments of destruction pulse sequence length according to heart rate. The ability to trigger destruction pulses and imaging pulses at different time points in relation to the ECG is today technically possible with the Sonos 5500, but the destruction pulse sequence length is not automatically adjusted according to heart rate variations.

The ultrasound contrast agent could be administered as a bolus injection or by infusion, when performing the method of the invention. Preferably the contrast

agent is administered by infusion. By applying high energy pulses according to the invention, a local bolus effect is created, enabling assessment of the perfusion. Using the method in combination with bolus administration may be of interest if wanting to start destruction, in order to come back to baseline, at the R-wave without further assessment of wash-in.

While the preferred embodiment of the present invention has been shown and described, it will be obvious in the art that changes and modifications may be made without departing from the teachings of the invention. The matter set forth in the foregoing description and accompanying drawings is offered by way of illustration only and not as a limitation. The actual scope of the invention is intended to be defined in the following claims when viewed in their proper perspective based on the prior art.

Examples

In vivo and in vitro studies were performed to better understand what parameters affect the occurrence of cardiac arrhythmias when performing triggered contrast echocardiography. A successful model was established, different ultrasound scanners and imaging parameters were tested and compared to in vitro measurements, and an imaging protocol for minimising the risk of trigger induced arrhythmias is suggested.

Example 1.

In vivo study

To investigate this phenomenon, to see if a triggered imaging protocol that did not induce VPBs could be developed, Triggered Contrast Echocardiography (TCE) was conducted in mongrel dogs (Body weight: 9-32 kg, mean: 22kg). The animals were anaesthetized with fentanyl and pentobarbital and mechanically ventilated with a respirator using room air. The protocol was approved by the local ethics committee and all procedures were terminal and performed according to current guidelines and regulations.

Three ultrasound scanners with four cardiac transducers were used. The scanners were a Philips HDI 5000 with P3-2 and P4-2 transducers (Andover, MA, USA), a Siemens Sequoia 512 with 3V2c transducer (Mountainview, CA, USA) and a Philips Sonos 5500 with S3 transducer (Andover, MA, USA). Various imaging modes, MIs and triggering protocols were tested during infusion of Sonazoid™ (Amersham Health). The infusion rate was 2-5 ml Sonazoid™ per hour (2-7 times clinical dose). The dose was adjusted for maximum contrast enhancement without significant shadowing. Except for a shorter focal depth and a modified infusion procedure, all US machinery and protocols were identical to procedures used in a clinical setting.

Standard 3-lead ECG connections were placed on the extremities and the best ECG lead chosen for trigger signal and display on the US machine. All US images and associated ECG tracings were recorded continuously on videotape. Imaging

was performed through the chest wall with the transducer mechanically fixated. The imaging plane was transverse mid-papillary. Each transducer was tested at max MI during SHI, triggered in end systole every eighth heartbeat. Other settings were: minimum image depth and a single focal point 4 cm deep. Ultraharmonics and Power modulation was tested in addition to SHI with the S3 transducer. With the P4-2 transducer the Triggered replenishment imaging (TRI) protocol with pulse inversion (flash MI: 0.8, 1.0 and 1.2, imaging MI: 0.4) was tested in addition to SHI. With the P3-2 transducer the effect of changing the trigger delay after the R-wave of the ECG complex, the triggering interval and the MI was also studied.

The transducer settings were kept constant for 25 to 200 triggering points when acquiring VPB frequency data. The shortest observation time was used when testing the effect of variations in trigger delay, since the variation from one tested setting to the next was small (40ms in the most sensitive area). The longest observation time was used when comparing transducers and imaging modes.

In vitro study

The output from each transducer at each setting was measured with a GEC-Marconi 0.5mm bilaminar hydrophone (Chelmsford, UK) at 4 cm depth in a water bath. The output from the hydrophone was connected to a calibrated preamplifier which was connected to a LeCroy 9310A oscilloscope (Chestnut Ridge, NY, USA). 100 pulses were sampled at 100 Msamples/s for each transducer setting. The data were transferred to a PC for offline analysis in MATLAB (Natick, MA, USA).

RESULTS

In vivo

VPBs were observed in all animals after careful positioning of the transducer. The optimal imaging plane for VPB studies could not be identified by anatomical structures alone, but had to be guided by TCE with the settings most likely to elicit VPBs. When switching transducers, careful comparison with the previously videotaped imaging plane was performed to get the least possible variations in the imaging plane.

Figure 5 shows an example of an ECG-trace captured from video tape. The VPB displays an abnormal QRS complex right after the trigger point indicated by the small vertical line.

Figure 6 shows VPBs per triggering event for each transducer at maximum MI (from left to right the MI were 1.9, 1.5, 1.5, 1.3, 1.5, 1.3 and 1.1). Four imaging modes are listed for the Sonos 5500 with the S3 transducer. SHI was used for the other transducers. The figure shows the mean frequency of VPBs ± one standard deviation for the different transducers and imaging modes tested in six animals. The codes after the name of the S3 transducer indicate the imaging mode. O1 is 2nd harmonic, T2B is Ultra-harmonics with a center transmit frequency of 1.3 MHz, T3A and T3C are Power Modulation at 1.9 and 2.5 MHz respectively. The P3-2 and P4-2 were operated in HPEN-mode and the 3V2c in H3.5-mode.

Figure 7 gives frequency of VPBs as a function of displayed MI, showing the same data as a function of MI and with added results for the P3-2 transducer at MIs of 1.2, 1.1, 0.8 and 0.4. The transducer with the highest MI, the 3V2c, gave no arrhythmias in any of the tested animals. The Philips HDI 5000 with the P3-2 transducer gave the highest frequency of arrhythmias. This transducer was then used to investigate other parameters which were suspected to influence the amount of VPBs.

Figure 8 gives VPBs per triggering event as a function of triggering interval (1:n) in heartbeats. The observation time per trigger interval was n minutes. n=0 indicates live imaging observed for one minute. The Figure shows the effect of varying the end systolic triggering interval from one image every heartbeat to one image every twentieth heartbeat. The results are from four animals, using the P3-2 transducer at an MI of 1.3. A plateau seems to be reached when triggering every twelfth cardiac cycle. This shows a dose dependency on the probability of eliciting an arrhythmia after a triggered image, since the contrast agent in the imaging plane is destroyed by each high MI imaging pulse, and it takes approximately 12 heartbeats to completely replenish the contrast in the myocardium.

Figure 9 shows the same data as Figure 8, but it is plotted as the frequency of VPBs instead of the probability of a VPB occurring after a triggering event. Triggering every fifth heartbeat gives the highest frequency of arrhythmias.

Figure 10 gives the frequency of VPBs as a function of relative trigger delay after the R-wave. A sample ECG-trace is drawn above the graph for reference.

1:5 triggering was used to minimise the observation time when testing the effect of variations in trigger delay after the R-wave. This was tested in four animals with the P3-2 at an MI of 1.3. The results are plotted in Figure 10 as a function of triggering delay relative to the R-waves. 0 indicates the peak of the first R-wave, approximately 0.3-0.4 is end systole and 1 is the peak of the next R-wave. There were large variations in the frequency of arrhythmias for each animal, but none of the animals had any VPBs in the beginning of systole, when the heart is in a refractory phase.

No adverse events following the VPBs were observed in any of the animals.

In vitro

Figure 11 shows the frequency of VPBs as a function of measured MI, and Figure 12 shows the frequency of VPBs as a function of measured energy in each pulse.

To investigate the differences between the results for each transducer, the output from each tested transducer setting was measured in vitro. Plotting the results from Figure 7 as a function of measured, derated MI correlates better with the observed frequency of VPBs, as shown in Figure 11.

Figure 13 shows the frequency of VPBs as a function of measured energy in each imaging frame.

Figure 14 shows Hydrophone measurements of the SHI (top) and the strongest Power Modulation (middle) pulses from the S3 and the SHI pulse from the P3-2 (bottom).

Mechanical index is not a good measure for bubble destruction. Similarly it seems that the acoustic energy in the transmitted pulse is a better predictor of VPBs as

shown in Figure 12, and seemingly even better is the integrated energy in each frame, measured at a single point, as shown in Figure 13. The larger spatial pulse overlap observed in each frame with the P3-2 transducer means that a large amount of energy hits each contrast agent micro bubble per frame. The outlier result from the Sonos 5500 scanner at (1400, 0.02) is the result from the SHI mode. The pulses in this mode differ from the other measured pulses by the low frequency (1.3 MHz vs. 1.6 to 2.3 MHz for the other transducers/settings), the long pulses (4.1 μs vs. 1.2 to 3.0 μs), different harmonic content and a more rectangular envelope compared to the other pulses' more Gaussian shape, suggesting that there is a more complex optimal predictor for the probability of eliciting VPBs than the integrated energy alone. See Figure 14 for a comparison of the transmitted pulses for the two imaging modes used with the Sonos 5500 scanner and the SHI pulse from the HDI 5000 with the P3-2 transducer.

Flash imaging

As flash imaging, or destruction wash in imaging, is starting to be a more used method for perfusion imaging with ultrasound contrast agents, the TRI protocol with the P4-2 was tested in three animals, with high MI triggered imaging using the P3-2 as a positive control. The results are shown in Table 1. Only three VPBs were observed during TRI. Ordinary triggered imaging with the P3-2 transducer gave a VPB frequency two orders of magnitude higher.

Table 1

Tx	Trigger interval	MI	# of triggers	# of VPBs	VPBs/ trigger
P4-2	1:8	0.8	3155	1	$3.2 \cdot 10^{-4}$
		1.0	3348	0	0
		1.2	3335	2	$6.0 \cdot 10^{-4}$
	1:1	0.4	68862	0	0
P3-2	1:8	1.3	544	24	0.044
		1.2	302	14	0.046

Claims:

1. Method of triggered ultrasound imaging of the myocardium of a human or non-human animal subject administered with an ultrasound contrast agent wherein at least one high mechanical index ultrasound pulse sequence is initiated such that the first pulse of said sequence falls within the Q-R-S interval of the electrocardiogram (ECG) the myocardium.

2. Method as claimed in claim 1 wherein the first high mechanical index ultrasound pulse coincides with the R-wave of ECG of the myocardium.

3. Method as claimed in claim 1 or 2 wherein in addition low mechanical index imaging pulses are initiated after the at least one high mechanical index ultrasound pulse sequence.

4. Method as claimed in claim 3 wherein the low mechanical index imaging pulses are initiated at or around a T-wave of the ECG of the myocardium.

5. Method as claimed in any of claims 1 to 4 wherein the ultrasound technique used is selected from destruction-wash-in imaging, triggered replenishment imaging and real-time perfusion imaging.

7. Method as claimed in any of claims 1-6 used in assessments of cardiac perfusion.

8. Use of an ultrasound contrast agent in a method as claimed in any of the preceding claims.

9. Use of an ultrasound contrast agent in the manufacture of an image-enhancing composition for administration to the vascular system of a human or non-human animal subject in order to measure or assess the perfusion of the myocardium in a method wherein at least one high mechanical index ultrasound pulse sequence is initiated such that the first pulse of said sequence falls within the Q-R-S interval of the ECG of the myocardium.

Abstract

The invention relates to a triggered ultrasound imaging method for imaging of the myocardium, minimizing the risk of eliciting cardiac arrhythmia. Particularly, the invention is directed to a method of assessing cardiac perfusion. Destruction pulses are triggered such that they coincide in time with the R-wave of the ECG of the myocardium, while imaging pulses are triggered during end-systole.

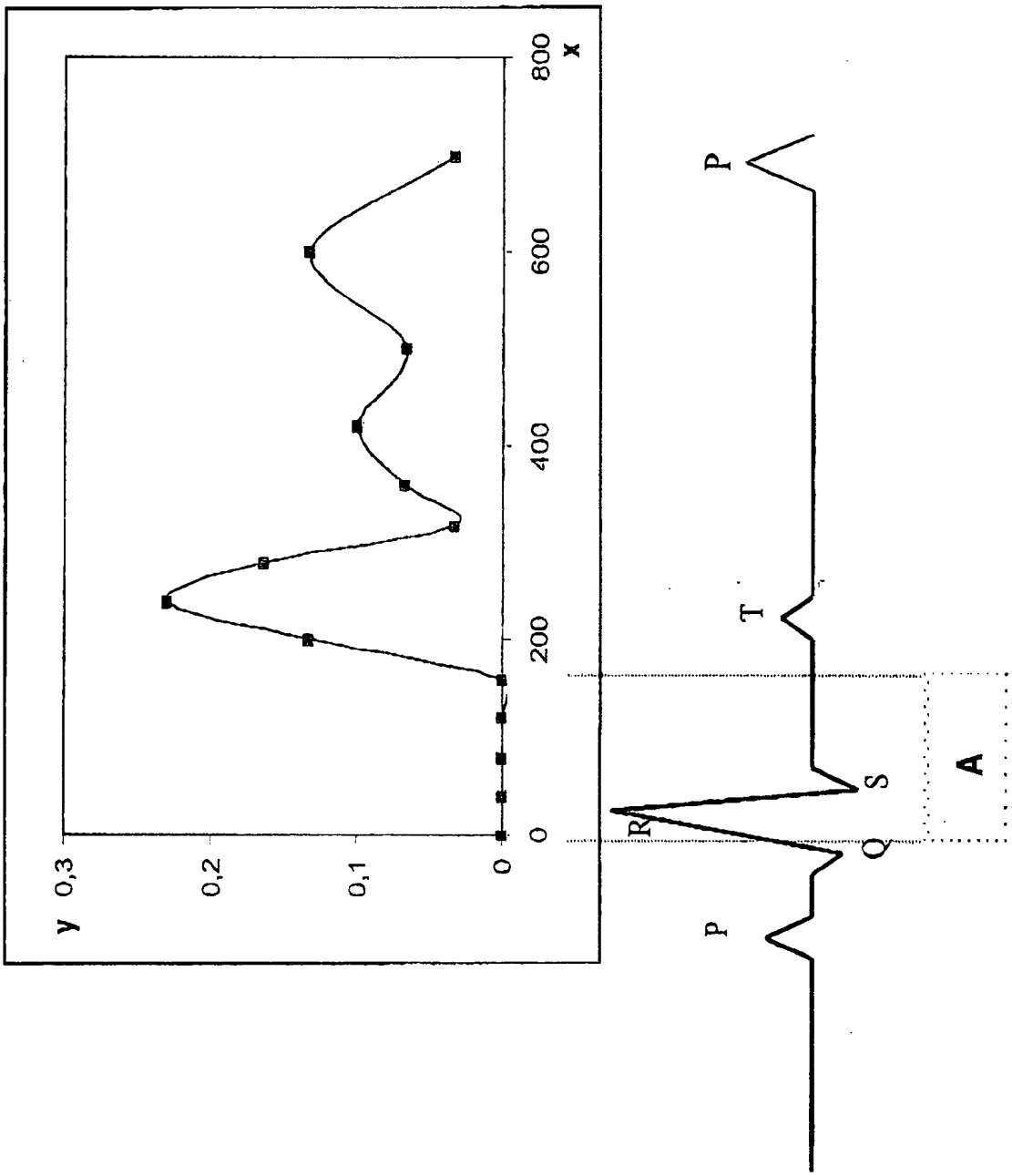


Figure 1

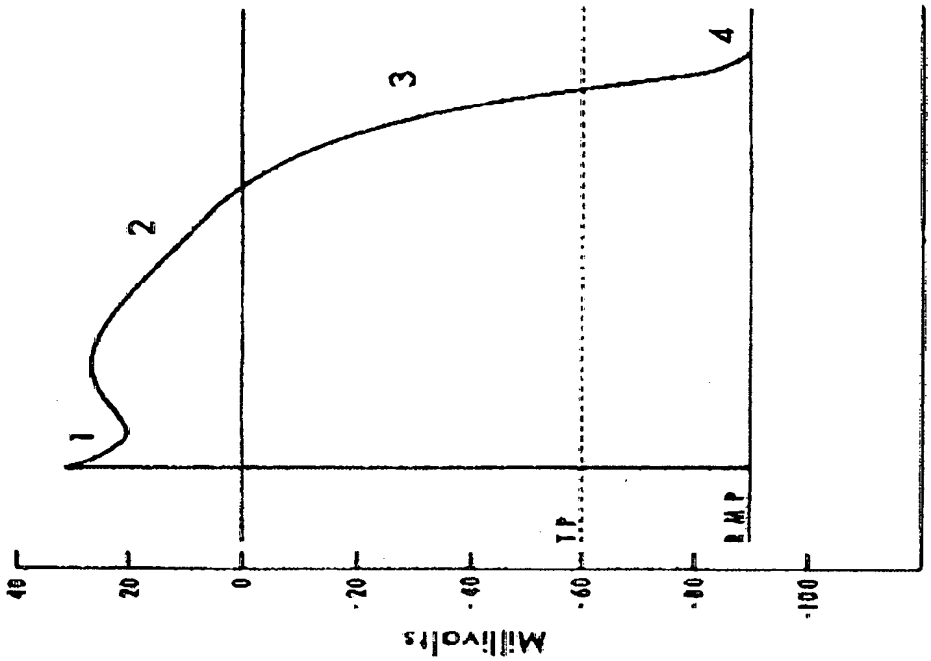


Figure 2

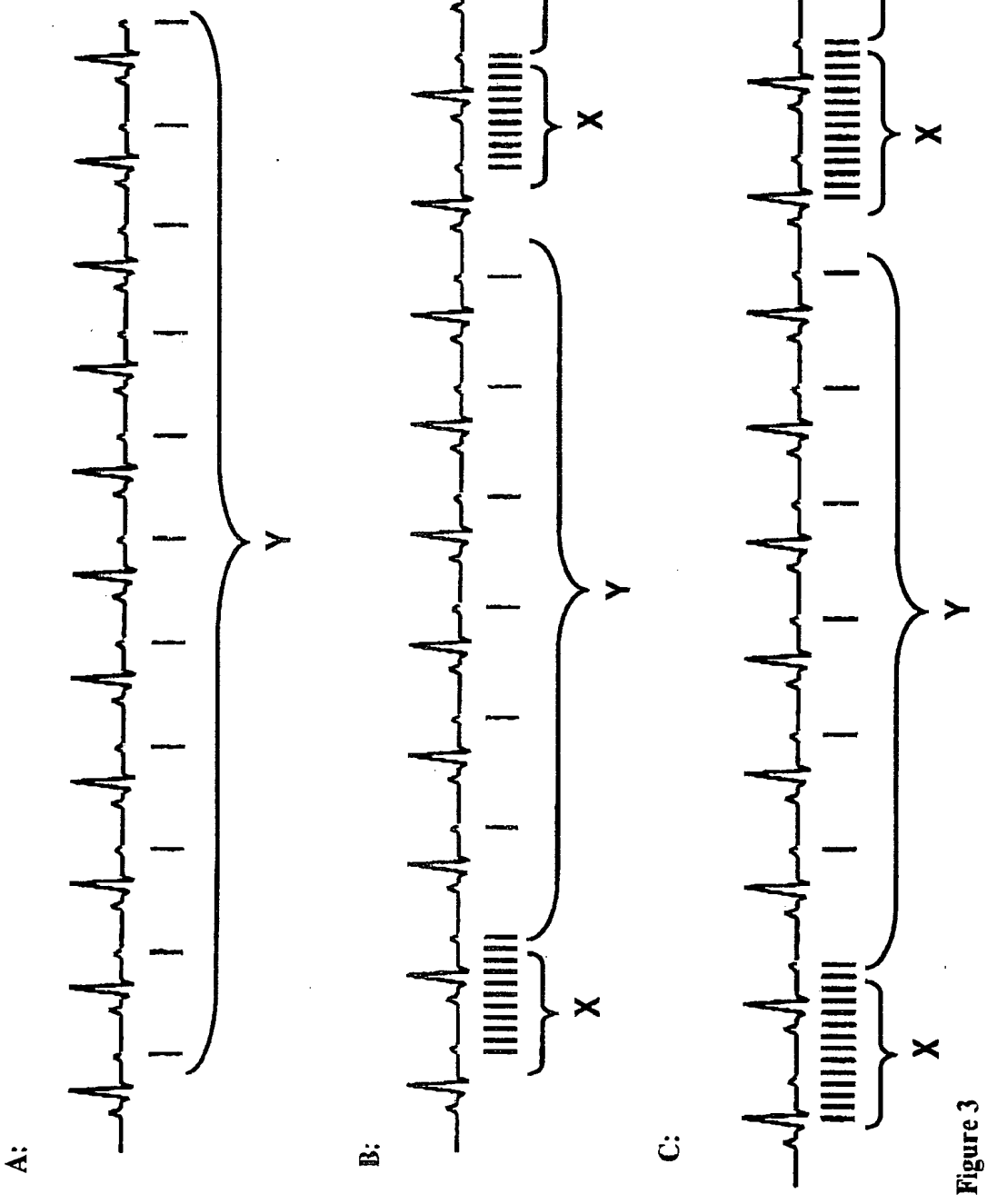


Figure 3

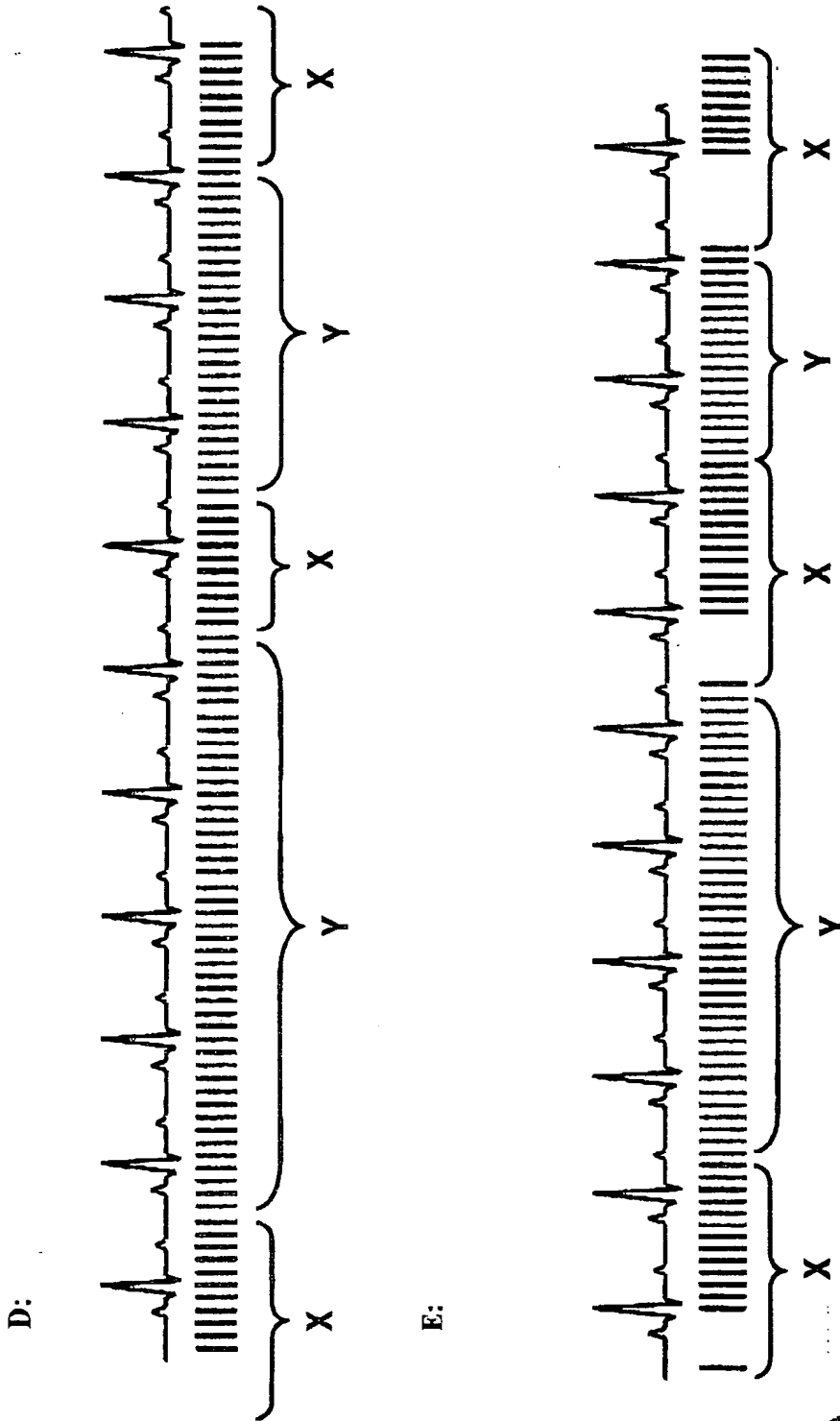
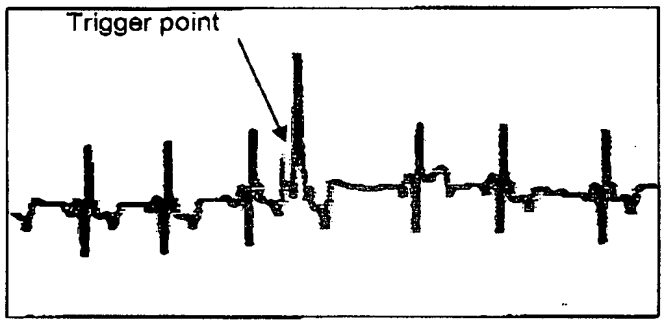


Figure 4

Figure 5.



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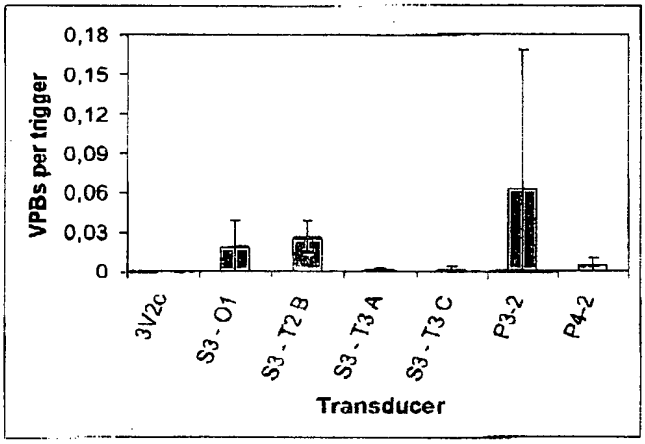

Figure 7.

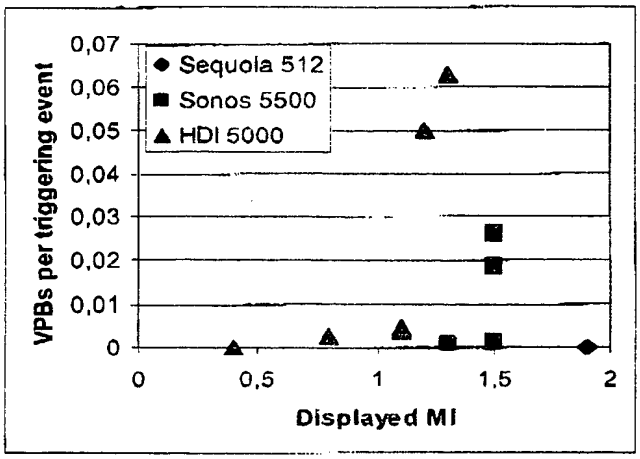

Figure 8.

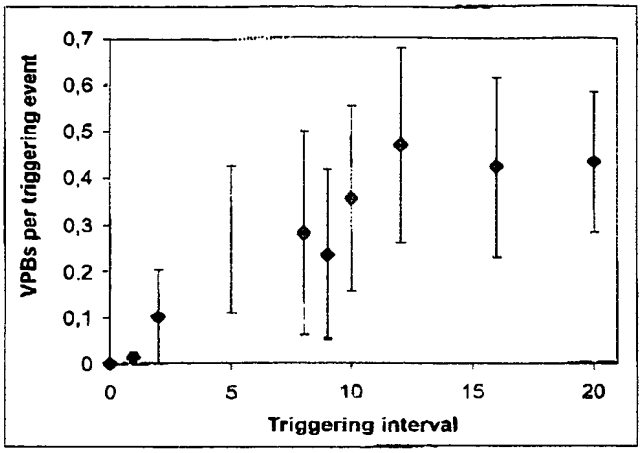

Figure 9.

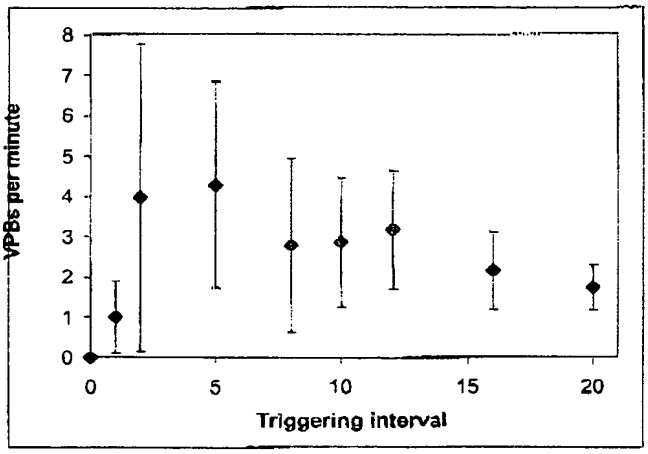

Figure 10.

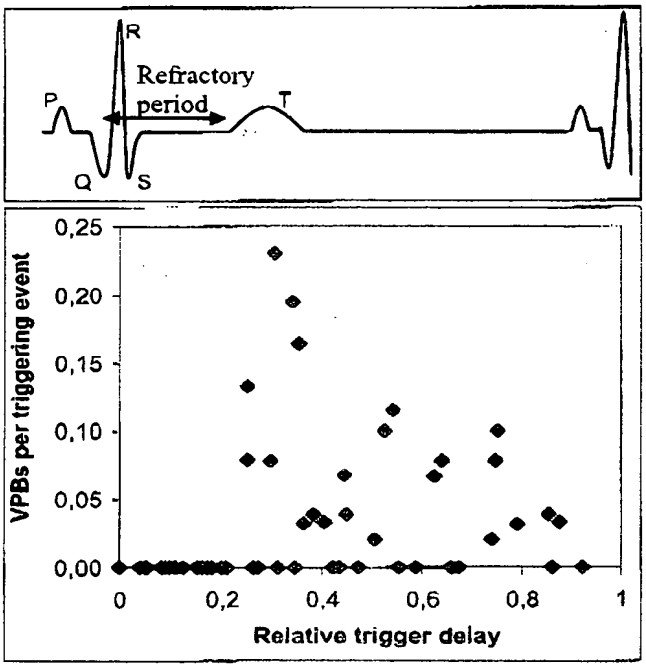

Figure 11.

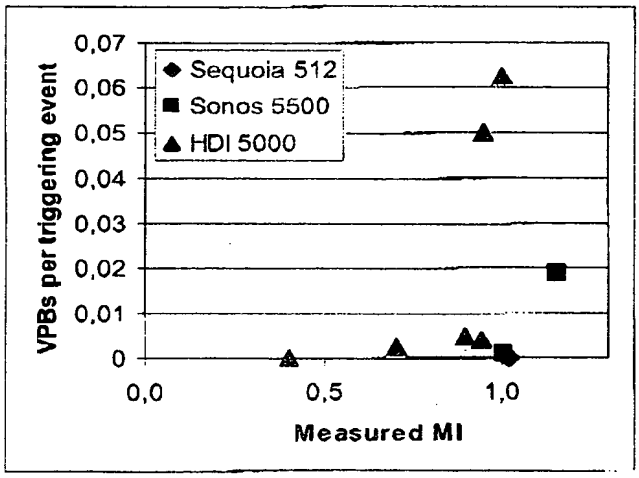

Figure 12.

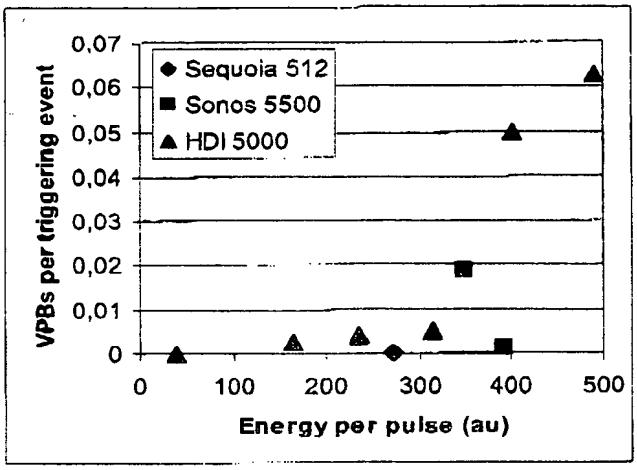

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Figure 13.

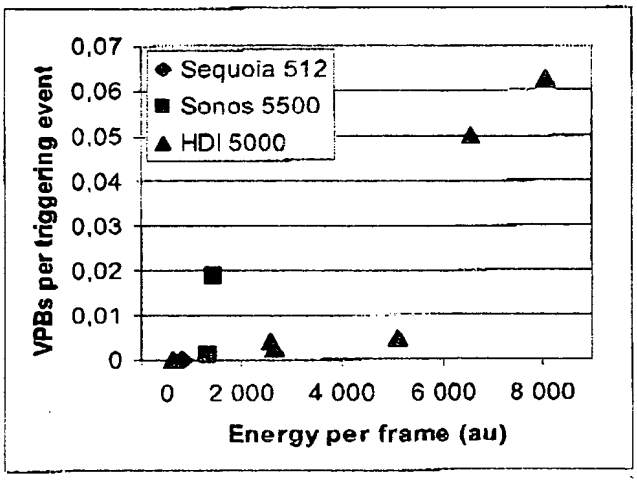

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Figure 14.